REMARKS

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, 52-55, and 57-59 are pending. Claims 15, 21, 48, and 57-59 have been amended to further clarify the subject matter claimed. No new matter is introduced.

Applicants respectfully request the Examiner to consider and withdrawal the rejections in view of the arguments below.

Withdrawal of Rejections

Applicants thank the Examiner for the withdrawal of the previous rejections set forth under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 103(a)

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over **Stephens** in view of **Salfeld**, **den Broeder**, further in view of **Kempeni** (all of record). Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

"As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(A) Determining the scope and content of the prior art; and

(B) Ascertaining the differences between the claimed invention and the prior art; and

(C) Resolving the level of ordinary skill in the pertinent art.

. . .

The question of obviousness must be resolved on the basis of these factual determinations. . . As stated by the Supreme Court in *KSR*, 'While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1391.'" (MPEP 2141, Section II, underline emphasis added)

Applicants' previous Office Action response first sought to clearly establish the first *Graham* factual inquiry - determining the scope and content of the prior art - with respect to *each* of the relevant citations. Applicants then argued that, based on such *Graham* factual inquiries, a legal conclusion of obviousness cannot be made.

The Examiner appears to have misunderstood Applicants' framework of analysis. For example, in response to Applicants' factual inquiry regarding the **Stephens** reference, the Examiner argues that "applicant is arguing against the Stephens reference individually" (page 3, the 2nd to the last paragraph of the Office Action).

For the benefit of the record, Applicants respectfully traverse the following statements in the Office Action concerning the scope and content of the cited prior art references.

The Stephens Reference (Primary Reference)

Examiner's Statement: "Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571" (most recently in page 3, lines 7-9 of the 12-7-09 Office Action)

Examiner's support: Applicants respectfully submit that the extent of the Examiner's support for the above statement lies in the following quoted passage in Stephens: "First infusion - *Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment with maximum patient response after 10 mg/kg . . . All patients who received CDP571 scored a reduction in pain scale by week 1.*" (Stephens, pages 327, 1st para., emphasis added).

Applicants' arguments: Applicants submit that there is no evidence of any symptom relief for the 0.1 mg/kg CDP571 treatment group described in Stephens that is commensurate with the required elements of the claims. Therefore, despite the fact that a sub-group of patients received CDP571 at a dose of 0.1 mg/kg, the data provided in Stephens suggests that there is no demonstrated benefit for these patients. As such, one of ordinary skill in the art would not conclude that Stephens "teaches" a method of treating RA using such a low dose (0.1 mg/kg) of humanized anti-TNFα antibody CDP571, as the Examiner suggests. Indeed, the Examiner appears to be disregarding the specific symptoms that are described in the pending claims, and equating them with different indices (*e.g.,* pain) described in Stephens.

Applicants' arguments are supported by the following facts:

(1) Stephens does not show any results, let alone any alleviation of the symptoms recited in the claims, for the treatment group receiving 0.1 mg/kg CDP571 (see Tables 2 & 3 on page 328 of Stephens). Indeed, the whole section (pages 327-330 of Stephens) discussing the results after the **first infusion** never explicitly refers to any data in the 0.1 mg/kg group (also see points (2) and (4) below).

(2) The "dose-dependent effect" statement relied upon by the Examiner should be fairly read to refer only to the 1 mg/kg and 10 mg/kg groups, not the 0.1 mg/kg group. For example, with respect to "**Swollen Joints**" (which most closely correlates to the "mean arthritic score" defined on page 27 of the specification), Table 2 shows steady trending worse in the 1 mg/kg group from pre-infusion to week 8, while the placebo group does not become worse until after week 4. The **CRP** data for the 1 mg/kg group shows "flare up" to baseline level at week 8 after an initial "dip," while there is steady improvement (decrease in value) in the placebo group (from 80 mg/l to 31 mg/l) (see Table 2). Likewise, the **Pain Score** described in Table 2 increased less (6.2-8.5, or 37%) in the placebo group compared to the 1 mg/kg group (5.5-8.3, or 51%). The only arguable effect in the 1 mg/kg group, albeit slight at best, is in **Tender Joint Score** after week 2 (see Table 2). Thus, in at least 3 of the 4 indications analyzed, the 1 mg/kg group appears to perform no better than the placebo group. In view of the marginal (if any) effect in the 1 mg/kg group, one of skill in the art could only conclude that the 0.1 mg/kg treatment group likely has no effect compared to the placebo group.

(3) Consistent with point (2) above, the 0.1 mg/kg treatment group was dropped all together in the second, third, and fourth injections (see pages 329-330 in Stephens).

(4) The "pain scale reduction by week 1" statement relied upon by the Examiner is largely irrelevant, and is taken out of context. Applicants submit that "all patients" likely refers to "all patients in the 10 mg/kg treatment group," not "all patients receiving CDP571 injection." In page 327, last paragraph of Stephens, immediately preceding the "all patient" statement, the paragraph first discusses the symptom improvement for **Tender Joint Score** (the 1st listed symptom in Table 2) in the 10 mg/kg group, then discusses symptom improvement for **Swollen Joints** (the 2nd listed symptom in Table 2) in the 10 mg/kg group. It is merely logical that the paragraph then discusses the 3rd listed symptom in Table 2 - **Pain Score**, for the 10 mg/kg group. In fact, the sentence immediately following the "all patient" statement for week 1 further explains the extent of pain score reduction (40%) by week 2, and persisting improvement by week 8.

(5) Even assuming, for the sake of argument, that there is pain score reduction by week 1 for all patients injected by CDP571, the significance of such observation is undermined by the fact that there is pain score reduction by week 1 even for the placebo group. In fact, comparing the pain scores for the placebo group with that of the 1 mg/kg group, the placebo group fares even better at weeks 4 and 8.

The above evidence strongly supports Applicants' position that Stephens fails to demonstrate any effect, let alone any alleviation of the symptoms recited in the claims, for the 0.1 mg/kg treatment group. This renders moot the Examiner's arguments that "one of ordinary skill in the art would be far more interested in the effect of the CDP571 antibody one week after infusion," and that "the decrease in pain score for the patients receiving 1 mg/kg CDP571 was still greater," since the data does not show any "effect" at all for the 0.1 mg/kg group. This conclusion is consistent with the "global assessment of disease activity" for the 1 mg/kg and 10 mg/kg groups (referred to by the Examiner), since such groups only have "borderline" statistical significance versus the placebo.

Furthermore, the significance of the CRP data in the 1 mg/kg and 10 mg/kg groups is unclear, because the placebo group patients have an average pre-infusion CRP level of 80 mg/l, much higher than the 37 mg/l of the 1 mg/kg group and the 50.5 mg/l of the 10 mg/kg group. Plus, as argued above, the placebo group CRP level shows steady improvement over the course of the 8 weeks, while the 1 mg/kg group reverted to the starting level after 8 weeks. If the 1 mg/kg group already shows marginal effect in terms of CRP, it is unclear how one of skill in the art would predict the effect of 0.1 mg/kg when the dose is reduced by a further 10-fold.

In summary, proper factual inquiry with respect to **Stephens** should have led one of ordinary skill to the conclusion that Stephens does not teach the treatment of arthritis with a single dose of 0.1 mg/kg humanized anti-TNFα antibody such that the arthritis is treated as demonstrable by mean arthritic score (claims 15 and 42), such that at least one symptom selected from the group consisting of joint distortion, swelling of the joints, joint deformation, or ankylosis on flexion is alleviated (claims 15 and 42), or such that the at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity is alleviated (claims 21 and 48).

The Salfeld Reference

Applicants' position is that **Salfeld fails to disclose "a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week**. The Examiner agrees that "it is true that Salfeld recites that an anti-TNFα antibody having the properties recited in the instant claims can be used to treat diseases when administered within the range of 0.1-20 mg/kg, and that Salfeld recites this dosage range without concurrently reciting a frequency of administration."

Applicants also respectfully submit, which the Examiner does not dispute, that the only time an administration frequency is recited with a dose range in Salfeld is in Example 4, part D, section III (col. 43, lines 6-8), where a thrice a week frequency is used: "[e]ach group received three i.p. injections per week of the indicated treatments" (emphasis added). The minimal dose tested in this experiment is 1.5 mg/kg (col. 43, line 2).

The den Broeder Reference

All enrolled patients in den Broeder were either administered D2E7 once every two weeks or once every four weeks, and the smallest dose administered was 0.25 mg/kg (see page 640, left column of den Broeder). In addition, den Broeder states, on page 641, left column that "one could speculate that even further reduction is possible for individual patients. This is supported by the remarkable long duration of response seen in some patients after only one administration of anti-TNF-α, documented for both D2E7 (up to 14 weeks EULAR response) and infliximab …"

Applicants' position is that **den Broeder never actually teaches or suggests the use of a human anti-TNFα antibody "in a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week" as required by the claims**, and the Examiner does not dispute this fact.

Instead, the Examiner appears to argue that it is possible that at least one of the 3 patients receiving 0.25 mg/kg dose were on once-per-4-weeks regimen, which allegedly is equivalent to "0.0625 mg/kg at a frequency of not more than once per week." Applicants traversed this assertion by arguing in the previous response that this is a mere theoretical *possibility* rather than *fact*, and that, in relying on the math to support this assertion, the Examiner appears to have ignored the Stephens teaching that lower doses of antibodies tend to clear faster from circulation (see Figure 1 in Stephens), have a shorter serum half life (see Figure 2 of Stephens), and trigger more pronounced anti-idiotypic antibody reaction (see Figure 3 of Stephens). The Examiner did

not respond to this argument in the instant Office Action. Further, regarding the den Broeder "speculation" that even lower doses is possible, Applicants argued in the previous response that den Broeder does not teach or suggest how much lower the combined dosage and frequency can go without completely foregoing the benefit of the treatment.

The Kempeni Reference

Applicants submitted, in the previous response, that Kempeni does not make up for the deficient teachings of the primary reference (Stephens) alone or in combination with the secondary references (Salfeld and/or den Broeder). The Examiner did not dispute this position in the instant Office Action.

Legal Analysis

Based on the *Graham* factual findings above, Applicants submit that **Stephens** at best teaches a lower effective dose of 1 mg/kg for CDP571 injection, and provides no evidence that the *tested* 0.1 mg/kg dose is actually *effective* compared to placebo at alleviating any of the symptoms required by the claims; **Salfeld** suggests a wide dosage range of between 0.1-20 mg/kg, with the only relevant disclosure about frequency being three times a week, and each time at doses at least 15-150 fold higher than the claimed range; **den Broeder** discloses that, in some patients, an effective dosage can be as low as 0.25 mg/kg when administered at an undisclosed interval, and further "speculates" (without providing any guidance) as to how much lower the dosage can go.

Since Stephens has already suggested that there is no demonstratable effects at 0.1 mg/kg, and since Salfeld has exemplified an effective dose of at least 45-fold (3 times 15) higher than "0.1 mg/kg for no more than once a week," one of skill in the art would have had no reasonable expectation that the presently claimed invention would be effective despite the "speculation" in den Broeder.

In summary, none of the cited art (taken alone or in combination) teaches or suggests the recited dosage and frequency limitation of Applicants' claims. The humanized antibody regimen disclosed in Stephens uses a dose 10-100 times higher (1 mg/kg) than the recited dose to achieve **marginal** results. Even assuming, for the sake of argument, that one of ordinary skill in the art would be motivated to replace such humanized antibody in Stephens with the fully human

antibody of Salfeld, there is no guidance regarding the dosage level *and* the accompanying administration frequency in Salfeld. den Broeder also does not remedy this deficiency. Therefore, the combined teachings of the cited art fail to disclose all of the limitations of the presently claimed invention. A *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph - Scope of Enablement

Claims 21, 22, 24, 31, 34, 35, 42, 43, 45, and 57 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable to the full scope of the claims. Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

Firstly, the Examiner argues that one cannot practice the invention claimed in claims 34, 35, and 45 because "applicant has not provided objective evidence that the D2E7 anti-TNFα antibody taught, e.g., by Salfeld, is the same thing as the *currently* commercially available HUMIRA (adalimumab) antibody." The Examiner further argues that the web site Applicants provided does not show when HUMIRA was first commercially available, and whether such date precedes the date of invention.

In this regard, Applicants note that one of the cited references, den Broeder, states on page 639, left column that D2E7 is "adalimumab (the generic name for HUMIRA)," and that the D2E7 used in the study was obtained from Knoll (Ludwigshafen, Germany). Applicants further note that "references to the biological material in printed publications" as well as "commercial availability" is indicia that a biological material is "known and readily available to the public." MPEP 2404.01. Thus, Applicants submit that "D2E7" is the same as the currently commercially available HUMIRA (adalimumab) antibody, which is referenced in at least the cited prior art printed publications. In addition, HUMIRA was approved by the U.S. FDA and as of December 31, 2002 (more than 10 months before the filing date of the instant application). See the following FDA web site:

www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

Therefore, Applicants submit that claims reciting the D2E7 antibody are enabled.

Secondly, the Examiner argues that the claimed invention is not enabled with respect to the dose range of 0.01-0.1 mg/kg, because the Examiner states that the claims as amended are

not limited to administering the anti-TNFα antibody, or antigen-binding portion thereof, for at least 10 treatments at a frequency of not more than once per week.

Applicants agree with the Examiner's read of the amended claims. Applicants submit that the enablement of these claims is not predicated on the requirement of having at least 10 administrations. Rather, the claims (as amended in the case of claim 21) require at least one symptom to be alleviated, or rheumatoid arthritis be treated. Thus, if a patient has symptom alleviation after less than 10 treatments (and thus demonstrable after 10 treatments), or has RA that is treated after less than 10 treatments (and thus demonstrable after 10 treatments), the method would fall within the scope of the claims. In contrast, the alleged non-enabled embodiments, *e.g.*, those not demonstrable after 10 treatments, are excluded from the scope of the claims.

Applicants submit that the data in the instant specification provides a reasonable correlation between the presently claimed invention and the enabled scope, such that the enablement requirement is met. Reconsideration and withdrawal of the enablement rejections are respectfully requested.

Obviousness-Type Double Patenting Rejections

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57 are rejected under the judicially created obviousness type double patenting rejection over claims 1-7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69, and 70 of U.S. Pat. No. 6,509,015 in view of Stephens, Salfeld, den Broeder, and further in view of Kempeni (all of record). Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

The Examiner argues that the presently claimed invention is not patentably distinct from the recited claims of the '015 patent, for the reasons set forth above with respect to Stephens, Salfeld, den Broeder, and further in view of Kempeni. Applicants submit that the amended claims all require administration of a low dose of a human anti-TNFα antibody, or antigen-binding portion thereof, such that certain symptoms are alleviated. This combination is neither taught nor suggested by the cited references, alone or in combination with one another. As such, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to the amended claims, as described in detail above. As such, Applicants

respectfully request that the rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 on the grounds of non-statutory obviousness-type double patenting be withdrawn.

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57 are rejected under the judicially created obviousness type double patenting rejection over claims 1-10 of U.S. Pat. No. 7,223,394 in view of Stephens, Salfeld, den Broeder, further in view of Kempeni (all of record). Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

The Examiner argues that the presently claimed invention is not patentably distinct from the recited claims of the '394 patent, for the reasons set forth above with respect to Stephens, Salfeld, den Broeder, and further in view of Kempeni. Applicants submit that the amended claims all require administration of a low dose of a human anti-TNFα antibody, or antigen-binding portion thereof, such that certain symptoms are alleviated. This combination is neither taught nor suggested by the cited references, alone or in combination with one another. As such, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to the amended claims, as described in detail above. As such, Applicants respectfully request that the rejection of claims 5-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 on the grounds of non-statutory obviousness-type double patenting be withdrawn.

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57 are rejected under the judicially created obviousness type double patenting rejection over claims 17, 41, 79, 86, 103, 110, 115, 122, 127, and 134 of U.S. Ser. No. 11/233,252 in view of Stephens, Salfeld, den Broeder, further in view of Kempeni (all of record).

Applicants submit that since the '252 application has not issued as a patent, this rejection is only proper if it is a *provisional* double patenting rejection. Applicants respectfully request that they be able to address this rejection upon allowance of either the instant claims or those of the '252 application, at which time Applicants will determine the appropriateness of filing a terminal disclaimer.

Rejection Under 35 U.S.C. § 102(b)

Claims 58 and 59 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Le *et al.* (U.S. Pat. No. 6,277,969). The Examiner argues that Le discloses on col. 36, the first

two paragraphs a method for treating arthritis using infliximab "at a dose of 0.5 mg/kg, for example, once per week." The Examiner argues that this disclosure anticipates claims 58 and 59. Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

Applicants have amended claims 58 and 59 to further clarify the subject matter claimed. Amended claims recite a low dose of about 0.5 mg/kg administered at a frequency of not more than once per week.

When discussing Genus-Species anticipation situations, MPEP 2131.02 states that: "[w]hen the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990)." Applicants submit that *Ex parte A* applies here, and that Le cannot anticipate claims 58 and 59 because one of ordinary skill in the art cannot "at once envisage" the presently claimed invention in view of the disclosure of Le.

Specifically, Le purportedly disclose multiple dosage levels (with a broad range of 0.01 to 100 mg/kg, plus **42 specific possibilities** within the range: 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg) and multiple administration intervals (including at least **60 specific possibilities**: on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, or any combination thereof). Applicants note that the disclosed range contains an infinite number of possibilities. The allegedly anticipated combination - 0.5 mg/kg at no more than once per week - is merely a small fraction of the at least 2400 (if not an infinite number when the range and the "combinations thereof" are considered) possible combinations. Therefore, Applicants submit that the presently claimed invention cannot be "at once envisaged" by the broad disclosure of Le. Thus, Le cannot anticipate the presently claimed invention.

The Examiner further argues that col. 80-89 (including Table 16) of Le exemplifies the treatment of human arthritis patients with "about 0.5 mg/kg (1.0 mg/kg was used)" showing a

decrease in arthritis symptoms in these patients. Here, the Examiner apparently equates "1.0 mg/kg" as used in the example to "about 0.5 mg/kg" in the claims.

"In determining the range encompassed by the term 'about,' one must consider the context of the term as it is used in the specification and claims of the application. *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1326, 81 USPQ2d 1427, 1432 (Fed. Cir. 2007)." MPEP 2173.05(b). Applicants submit that the Examiner's interpretation of the term "about" is inconsistent with the instant specification even under the "broadest reasonable interpretation" standard during examination. Specifically, Applicants have tested multiple doses in the specification, including data for 0.5 mg/kg and data for 1 mg/kg. Under this circumstance, it is clearly improper to equate "about 0.5 mg/kg" to "1 mg/kg." Therefore, the disclosure in col. 80-89 (including Table 16) of Le does not support the Examiner's position.

Reconsideration and withdrawal of the rejection of claims 58 and 59 under 35 U.S.C. § 102(b) are respectfully requested.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 449-6500.

The Commissioner is hereby authorized to charge any fees associated with the filing of this communication to our Deposit Account No. **50-4876**, from which the undersigned is authorized to draw under Order No. **117813-99302**.

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Respectfully submitted,

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